

Treatment of Congenital Hypothyroidism

State and regional programs have been instituted in the United States and Canada for the screening of newborn infants for congenital hypothyroidism, and this topic was the subject of a recent report by the Committee on Genetics.¹ The incidence of this disorder—averaged in several large series—is approximately 1 per 5,000 live births; therefore, these screening procedures represent a major advance in preventive medicine. Based on 3,160,000 live births in the United States in 1974, approximately 600 new cases of congenital hypothyroidism will be diagnosed each year through these screening programs and by recognition of affected infants by individual practitioners. These screening procedures result in earlier recognition of the disorder and thus a younger age at diagnosis; there also is increased knowledge about thyroid hormone homeostasis in the fetus and newborn infant. Therefore, it is appropriate to review dosage recommendations for treatment of infants with congenital hypothyroidism. In general, these recommendations are applicable to infants and young children with hypothyroidism regardless of the cause.

Neonatal Physiology

Production of thyroid hormones by the fetus begins by midgestation. Because of limited transplacental transfer, fetal development is almost entirely dependent on endogenous production. The thyroid gland secretes thyroxine (T_4) and triiodothyronine (T_3). Most of the circulating T_3 is formed by peripheral monodeiodination of T_4 , although marked thyroid-stimulating hormone (TSH) stimulation also increases the levels of circulating T_3 . A recent major advance is the recognition that the fetus preferentially forms the metabolically inactive reverse T_3 (rT_3) from T_4 . At present, T_3 appears to be the biologically active thyroid hormone at the cellular level, and T_4 may be a circulating prohormone. For example, athyrotic adults treated with T_4 have T_3 levels similar to those in normal adults.²

There is a dramatic surge of TSH immediately after birth, and the blood levels of both T_3 and T_4

are elevated well above those in normal adults. Later during the first week of life, serum rT_3 begins to fall toward the lower levels characteristic of healthy children and adults.³ Because of these dynamic changes within a few days after birth, values for serum levels of thyroid hormones obtained in newborn infants must be compared to the normal range for the postnatal age at which they were obtained.³⁻⁵

Conversion of T_4 to T_3 in peripheral tissues is decreased when the patient has malnutrition postoperatively and in a variety of disease states. Serum levels of T_3 fall and rT_3 may rise. Thus, small-for-gestational-age or ill neonates may have changes in thyroid hormone levels which may be confusing. Such alterations may provide an important metabolic regulatory mechanism for the neonate, and there may be situations in which it is not clear whether a deviation from average is pathologic or physiologic.

Diagnosis

Screening tests use filter paper impregnated with a drop of blood obtained by heel stick, frequently obtained when phenylketonuria screening is performed. A radioimmunoassay procedure is used to determine total T_4 level; a TSH determination is made on low or borderline samples. Although initial studies appeared promising, screening of cord blood specimens for rT_3 is not practical because about 12% of the normal population would require retesting.⁶ Venous or capillary specimens for confirming tests are requested when the values fall below a defined limit, and confirmation usually consists of determinations of TSH level and a repeated T_4 measurement. Physicians caring for newborn infants should become familiar with the procedures recommended in their locale. Where no general screening program is in effect, physicians may elect to use commercial laboratories, some of which perform daily assays of T_4 on filter paper specimens (with TSH on borderline-low specimens) for a nominal cost (as little as \$3). The laboratory selected should be able to perform

reliable assays with rapid reporting of deviant values.

Mailing of specimens and processing by central laboratories require several days to a week or two, and treatment need not be delayed pending the results of confirmative tests. *Normal adult standards for T₄ must not be used to evaluate neonatal thyroid function. To do so may lead to failure to diagnose the condition with disastrous effects on prognosis.*

Clinical examination remains an important aspect of diagnosis and follow-up. This is particularly true because it has yet to be demonstrated from prolonged experience with large-scale screening programs that false-negatives will not occur. Complaints suggestive of hypothyroidism in neonates include such common, though usually innocent, symptoms as persistence of mild jaundice, skin mottling, constipation, slow feeding, and hoarse cry. Paradoxically, some infants have had diarrhea. These findings should prompt a complete physical examination without delay. Telephone management alone is not adequate.

Physical signs—present in approximately one-half the infants with hypothyroidism^{3,7}—include lethargy, hypothermia, feeding problems, failure to gain weight, respiratory problems, a large anterior and posterior fontanel, dry skin, thick tongue, hoarse cry, and umbilical hernia. If a goiter is present, it is diagnostic of thyroid disease, unless the mother has been treated with an antithyroid drug or iodides.

Definitive diagnostic studies are indicated in infants with suggestive historical and/or physical findings, and in whom early diagnostic efforts do not rule out hypothyroidism, whether or not the infant has been part of a screening program.

Infants with an ectopic thyroid gland, such as a lingual thyroid, may have adequate or borderline thyroid function for months or even years; therefore, a normal T₄ level in the neonatal period should not be considered absolute evidence against congenital abnormalities of the thyroid.

Laboratory Examinations

Infants with absent or inadequate thyroid function characteristically have a low T₄ level and an extremely elevated TSH level. Because there may be some overlap in T₄ values between normal and mildly hypothyroid infants, the finding of an elevated TSH level is more sensitive and reliable. Knee and ankle films for bone age may be helpful. The distal femoral epiphysis is not ossified in full-term infants with hypothyroidism. A technetium Tc 99m scan may reveal the absence of thyroid tissue, and it is preferable to the use of

iodine 131 for this purpose because the radiation dose is lower.

A diagnostic error can be made in the infant with hypothyroidism caused by pituitary insufficiency or hypothalamic dysfunction. The TSH level, which is elevated in primary hypothyroidism, will be reported as normal in these infants. Deficiencies of other pituitary hormones, if they are documented, will aid in the diagnosis.

Further diagnostic dilemmas include infants who may have a low T₄ level because of prematurity, hypoproteinemia, deficiencies in thyroid binding globulin, or illness from nonendocrine causes. The results of thyroid function tests frequently are confusing. When interpretation is difficult, the disease should be managed in consultation with a physician experienced in the diagnosis and treatment of thyroid disease in infants.

Initiation of Treatment

If the initial history and physical examination are suggestive, blood should be drawn for definitive thyroid studies (to include at least a determination of T₄ and TSH levels) and treatment begun promptly. When congenital hypothyroidism is suspected on clinical grounds, diagnostic efforts and treatment generally should not be withheld until the results of screening tests are received. Prompt treatment improves the prognosis for later mental development.⁶ There is no known risk in initiating appropriate replacement therapy; therefore, it seems safer to err on the side of beginning treatment, which can be discontinued if necessary when the results of thyroid function tests are available. If screening tests are abnormal, the physician should obtain blood for definitive tests and begin therapy while waiting for confirmation.

If a firm diagnosis cannot be made on the basis of the laboratory findings but there is a strong clinical suspicion of congenital hypothyroidism, a conservative approach would be to ensure euthyroidism with replacement therapy until 1 or 2 years of age. At this age, medication can be stopped and definitive diagnostic studies can be carried out; this treatment plan avoids the potential risk of the infant incurring serious, permanent brain damage.

Choice of Replacement Agent

A number of thyroid hormone preparations are commercially available. These include desiccated thyroid U.S.P., desiccated thyroid standardized by bioassay, thyroglobulin (Proloid), synthetic levothyroxine sodium (Synthroid, Letter), syn-

thetic T_3 (Cytomel), and a combination of T_4 and T_3 (Euthroid, Thyrolar).

The short half-life of T_3 allows for a more rapid escape from hormone action if complications occur during therapy. However, complications seldom occur in infants and children, so this characteristic of T_3 is not particularly advantageous. In fact, the short half-life of T_3 can produce undesirable fluctuating effects because of uneven action if doses are missed, as is likely during chronic therapy. Further disadvantages of preparations containing synthetic T_3 are the cost and the fact that measurements of serum T_4 level, the most generally available and reliable thyroid test, cannot be used to assess therapy.

The Committee on Drugs recommends synthetic levothyroxine as the drug of choice for the treatment of hypothyroidism. This product is inexpensive, frequently cheaper than an equivalent dose of desiccated thyroid of an acceptable quality. One hundred 0.05-mg tablets retail for from \$2 to \$5. Pediatric doses have been well established by clinical studies.^{6,7}

The United States Adopted Name should be used if the physician wishes to prescribe the medication generically. For the synthetic preparations these names are T_4 , levothyroxine sodium; T_3 , liothyronine sodium; $T_4:T_3$ combination, liotrix.

Initial Dose for Infants

Suppression of TSH to normal levels has been used as the criterion of a minimum dose in older children. *Normal TSH levels must not be used as the sole criterion of adequacy of dose in congenital hypothyroidism because the TSH level may remain elevated for months during replacement therapy with proper or even excessive doses of thyroid hormone.* The goal of treatment should be to maintain levels of T_4 appropriate for age throughout infancy and childhood.^{4,5,9} Maintaining the serum T_4 level in the upper half of this range makes it less likely that levels will fall to hypothyroid values between visits because of growth or during brief periods of noncompliance.

Treatment should be started at 0.025 to 0.05 mg/day in a single, oral dose in otherwise healthy, full-term, newborn infants. For most of these infants, 0.0375 mg is an appropriate dose. In premature infants weighing less than 2,000 gm and in infants at risk for cardiac failure, the starting dose may be 0.025 mg/day. The dose for these premature and at-risk infants can usually be increased to 0.05 mg in four to six weeks. If the patient is unable to take oral medication, T_4 may

be administered intravenously in a daily dose equal to 75% of the oral dose. Ordinarily, there is no increased hazard or advantage to intravenous administration. Each dose must be reconstituted shortly before administration.

There is no need to start the medication at less than full replacement and increase it gradually in newborn infants. However, adverse effects such as hyperactivity in an older child can be minimized if the starting dose is one fourth of the full replacement dose, and the dose is increased by one fourth weekly until full replacement is reached. Cardiac complications, such as arrhythmias and congestive heart failure, sometimes occur in adults with far advanced myxedema if initial treatment is too aggressive. These are not a problem in infants and children in whom treatment is begun relatively early in the course of the disease.

Secondary adrenal insufficiency must be considered when hypothyroidism is due to hypothalamic or pituitary disease. If adrenal insufficiency exists, glucocorticoid replacement should be initiated two days before T_4 is started to avoid precipitating an acute adrenal crisis.

Response to Therapy

Improvement in the infant's level of awareness, temperature control, and gastrointestinal motility should be evident within a few days, and become dramatic shortly thereafter. The infant should be watched during the first two weeks for cardiac overload, arrhythmias, and aspiration from avid suckling. In some profoundly hypothyroid infants, it will be preferable to initiate treatment in the hospital. A follow-up visit should be scheduled for six weeks after initiation of therapy. The full effects of the hormone will have been reached at this time. Further examinations should be performed at least at 6 and 12 months of age and yearly thereafter. Length should be plotted at each visit, and total T_4 level (and/or TSH level) should be measured when necessary to monitor compliance and assist in making dosage adjustments. Bone age may also be helpful in assessment.

Dose Adjustment

The doses of T_4 recommended for infants and children by some standard sources are excessive. Before learning that T_3 is formed outside the thyroid gland by monodeiodination of T_4 , it was thought that, when T_4 alone was given, higher levels were needed to provide an adequate hormone effect. This is now known to be fallacious, and the use of older dose tables for synthet-

ic T₄ may result in iatrogenic hyperthyroidism. Recent work^{10,11} has established appropriate doses for children more than 1 year old.

Normal growth is the best indicator of adequate treatment. A T₄ dose of 0.05 mg is generally adequate throughout the first year of life. After this, the dose should be increased to 0.003 to 0.005 mg/kg/day^{10,11} until the adult dose of about 0.15 mg is reached in early or midadolescence. Most adolescents and adults are euthyroid while receiving 0.15 mg in a single daily dose.¹² The definitive criterion of dose appropriateness is clinical euthyroidism; an occasional patient will require an unusual dose ranging from 0.1 to 0.3 mg/day. Although the laboratory values are helpful, they cannot be substituted for clinical judgment. Occasionally a patient will be seen who is clinically hyperthyroid or hypothyroid even though the serum total T₄ level is normal, as statistically defined. The dose for these patients should be adjusted on clinical grounds, or additional testing may be indicated.

Overtreatment is to be avoided. In the past, excessive doses have been recommended with the rationale that a slight underdose is harmful but a slightly excessive dose is not. The occurrence of minimal brain damage in children with thyrotoxicosis during infancy¹³ suggests that this assumption is probably fallacious. Further complications of excessive treatment are acceleration of bone age and premature craniosynostosis.

Drug Interactions

In both children¹⁴ and adults,¹⁵ hyperthyroidism accelerates and hypothyroidism slows drug metabolism. The magnitude of this effect usually is unknown, but it may be substantial. The possibility of drug toxicity at standard doses in hypothyroid patients and diminished drug effect in hyperthyroid patients must be kept in mind. Phenobarbital increases the clearance of thyroid hormones, and other enzyme inducers may have a similar effect. The dose of thyroid hormone may require adjustment when anticonvulsant therapy is initiated, adjusted, or discontinued. A number of drugs (e.g., heparin, phenytoin, and sex steroids) alter binding of T₄ to thyroid-binding globulin and other serum proteins. If the patient is under treatment with these drugs or has an abnormality of plasma protein levels, the total T₄ measurement may be misleading. Some, but not all, clinicians find the free T₄ measurement to be helpful in these patients. Final reliance may have to be placed on clinical judgment, which is aided by measurements of growth and bone age.

Conclusions

Screening for neonatal hypothyroidism represents an important advance in preventive medicine. The treatment of congenital hypothyroidism is effective, inexpensive, and not difficult for physician, parent, or patient. The likelihood of disability is always reduced and may be prevented.

Recommendations

The Committee on Drugs recommends the following:

1. Physicians caring for children should participate in state, regional, or provincial screening programs for hypothyroidism and should maintain a high level of clinical suspicion to assure the earliest possible diagnosis of congenital hypothyroidism.
2. Levothyroxine in a usual starting dose of 0.025 to 0.05 mg/day should be used for treatment.
3. Dose adjustments should be made on the basis of patient response, particularly growth and development, and by measurements of serum T₄ level, bone age, and/or other appropriate laboratory determinations.
4. Consideration should be given to interactions with other drugs and disease states so appropriate dose adjustments will be made.

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Consultants: John D. Crawford, M.D.; Jean H. Dussault, M.D., M.Sc.; A. B. Hayles, M.D.; Geoffrey P. Redmond, M.D.

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ABSTRACT

EKG Effects of Imipramine Treatment in Children, by Kishore R. Saraf, M.D, Donald F. Klein, M.D., Rachel Gittelman-Klein, Ph.D., Norman Gootman, M.D, and Philip Greenhill, M.D.

There are increasing reports of serious side effects in children with clinical use of imipramine in high doses. Our analysis of the EKG effects of imipramine in 25 hyperactive and 8 school phobic children suggests that children on a dose of imipramine of 3.5 mg/kg or more are likely to show an increase in PR interval of .02 seconds or more and that such increases are more likely to occur in patients with a small pretreatment PR interval. In 7 children the PR interval prolongation was above the rate-corrected norm. EKG monitoring seems desirable in children maintained on imipramine dose of 3.5 mg/kg or more. *J Am Acad Child Psychiatry* 17:60, 1978.

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